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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FLOOD, MICHELE C	
ART UNIT	PAPER NUMBER
1655	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/771,711	YOUNG, JEFFREY	
	Examiner	Art Unit	
	Michele Flood	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,8 and 26-73* is/are pending in the application.

4a) Of the above claim(s) *7,8 and 26-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Prosecution Application

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 8, 2008 has been entered.

Acknowledgment is made of the receipt and entry of newly added Claims 51-73.

Claims 51-73 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 51-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of Claim 51, lines 5-6, are rendered vague and indefinite by the phrase, "when said firs and said active ingredients are administered, insulin beta cells of said living object is substantially restored so as to achieve lowering of plasma sugar level" because it is unclear as to whether the claim-designated beneficial functional effects are attributable to the administering of berberine alone or the

co-administration of each of berberine and catalpol, since there is lack of clear antecedent basis for the recitation of "said active ingredients". The lack of clarity renders the claim ambiguous.

The term "substantially" in Claim 51 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

All other cited claims depend directly or indirectly from rejected claims and are, therefore, also, rejected under U.S.C. 112, second paragraph for the reasons set forth above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 51, 53, 54, 57-65 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jiang et al. (O or U; Translation of foreign patent document CN 1393264 A provided herein and referred to herein.) and Song et al. (V; Translation of foreign language document provided herein.) in view of Nishimura et al. (R), and further in view of Ebrup et al. (O), Gorogawa et al. (W) and Hamaoka et al. (X).

Applicant claims a method of treating a living object with non-insulin dependent diabetes, comprising a step of administering to said living object a composition comprising a predetermined amount of berberine as a first active ingredient and a predetermined amount of catalpol as a second active ingredient, in such a manner that when said first and said active ingredients are administered, insulin beta cells of said living object is substantially restored so as to achieve lowering of plasma sugar level. Applicant further claims the method, as recited in claim 51, wherein said composition further comprises an oleanolic acid as a third active ingredient; and, wherein said berberine is extracted from one or more natural herbs selected from the group consisting of Berberis, Chelidonium, Stephniz, Coptis, Phellodendron, and Ziziphus. Applicant further claims the method, as recited in claim 53, wherein said catalpol is extracted from one or more natural herbs selected from the group consisting of Rehmannia, Verbascum, Paulownia, Globularia, and Adonis. Applicant further claims the method as recited in claim 52, wherein said oleanolic acid is extracted from one or

more natural herbs selected from the group consisting of Olea, Swertia, Astrantia, Lonicera, and Beta. Applicant further claims the method as recited in claim 55, wherein said berberine is extracted from one or more natural herbs selected from the group consisting of Berberis, Chelidonium, Stephniz, Coptis, Phellodendron, and Ziziphus, and said catalpol is extracted from one or more natural herbs selected from the group consisting of Rehmannia, Verbascum, Paulownia, Globularia and Adonis. Applicant further claims the method, as recited in claim 51, wherein said composition is prepared into a predetermined form for administration that contains 1 to 300 mg/kg/dl of said berberine. Applicant further claims the method , as recited in claim 53, wherein said composition is prepared into a predetermined form for administration that contains 1 to 300 mg/kg/dl of said berberine; and, wherein said composition is prepared into a predetermined form for administration that contains 5 to 150 mg/kg/dl of said berberine. Applicant further claims the method, as recited in claim 59, wherein said composition is prepared as a draught in water; wherein said composition is prepared as a syrup; wherein said composition is prepared as a cachets; wherein said composition is prepared as a tablet; and, wherein said composition is prepared as a solution. Applicant further claims the method, as recited in claim 51, wherein said composition is prepared into a predetermined form for administration that contains 1 to 300 mg/kg/dl of said active ingredients. Applicant further claims the method, as recited in claim 52, wherein said composition is prepared into a predetermined form for administration that contains 1 to 300 mg/kg/dl of said ingredients. Applicant further claims the method, as recited in claim 54, wherein said composition is prepared into a

predetermined form for administration that contains 1 to 300 mg/kg/dl of said ingredients. Applicant further claims the method, as recited in claim 56, wherein said composition is prepared into a predetermined form for administration that contains 1 to 300 mg/kg/dl of said ingredients. Applicant further claims the method, as recited in claim 68, wherein said composition is prepared as a draught in water; wherein said composition is prepared as a syrup; wherein said composition is prepared as a cachets; wherein said composition is prepared as a tablet; and, wherein said composition is prepared as a solution.

Jiang teaches the oral administration of an effective amount of berberine (0.5g three times a day) extracted from the rhizomes of *Coptis* to humans suffering Type II diabetes to provide a method of treating a living object with non-insulin dependent diabetes and the lowering of plasma sugar level. *See* first paragraph of page 3 and page 10 and 11 of translation, as well as Table 2. Jiang further teaches the berberine ingredient as an insulin receptor sensitizer for the treatment of non-insulin diabetes and demonstrates its enhancement of the expression of peroxisome proliferator-activated receptor (PPAr) gene.

In another instance, Song teaches orally administering an effective amount of berberine (0.1 g) obtained from Radix *Coptis* to non-insulin dependent diabetic rats fed a high caloric diet to provide a method of treating a living object with non-insulin dependent diabetes and the lowering of plasma sugar level. Song further teaches that berberine inhibited hypersinsulinemia and ameliorated the abnormalities in glucose tolerance and lipid metabolism. The treatment taught by Song also decreased lipid

peroxide content and increased superoxide dismustase activity in the liver indicating that berberine has marked antioxidant activity and thus inhibits metabolic disorders resulted from oxidative damage in the non-insulin dependent diabetic.

The combined teachings of Jiang and Song are set forth above. The combined teachings teach the instantly claimed method except for administering catalpol as a second active ingredient. However, it would have been obvious to add the claim-designated ingredient to the method taught by the combined teachings of Jiang and Song to provide the instantly claimed method because at the time the invention was made Nishimura taught the extraction of *Rehmannia* to obtain catalpol having antidiabetic effect. At the time the invention was made, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to add the catalpol taught by Nishimura to the composition used in the method taught by the combined teachings of Jiang and Song to provide the instantly claimed invention because Nishimura taught that catalpol obtained from *Rehmanniae* was useful in the therapy of complications related to diabetes, such as cataract, retinopathy and renopathy. Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add the claimed ingredients in the making of the claimed method of treating non-insulin dependent diabetes in a subject in need thereof because it is well known that its *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re*

Pinten, 459 F. 2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi*, 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960).

The combined references do not specifically teach a method wherein the administering of the ingredients to a living subject provides the claim-functional effect for restoring insulin beta cells of the living subject so as to achieve lowering of plasma sugar level.

However, Ebrup teaches that compounds displaying peroxisome proliferator-activated receptor activation are useful in the treatment of type II diabetes and macrovascular complications associated with type II diabetes and metabolic system disorder by lowering both the overt hypertriglyceridaemia, hyperglycemia, impaired glucose tolerance, insulin tolerance, insulin resistance, obesity, cardiovascular disorders, and apoptosis of insulin beta-cells of islets of Langerhans. Thus, it was known in the art at the time of the invention that compounds which enhance the expression of the peroxisome proliferator-activated receptor gene, such as the berberine extracted from *Coptis* used in the method taught by Jiang, lower apoptosis of insulin beta-cells of islets of Langerhans and serum blood levels; and thereby are useful in the treatment and complications associated with Type II diabetes.

Secondly, Gorogawa teaches, " Oxidative stress is induced under diabetic conditions and causes various forms of tissue damage in patients with diabetes. Recently, pancreatic beta-cells have emerged as a putative target of oxidative stress-induced tissue damage and this seems to explain in part

the progressive deterioration of beta-cell function in type 2 diabetes. As a step toward clinical trial of antioxidant for type 2 diabetes, we investigated the possible anti-diabetic effects of probucol, an antioxidant widely used as an anti-hyperlipidemic agent, on preservation of beta-cell function in diabetic C57BL/KsJ-db/db mice. Probucol-containing diet was given to mice from 6 to 16 weeks of age. Immunostaining for oxidative stress markers such as 4-hydroxy-2-nonenal (HNE)-modified proteins and heme oxygenase-1 revealed that probucol treatment decreased reactive oxygen species (ROS) in pancreatic islets of diabetic animals. Oxidative stress is known to enhance apoptosis of beta-cells and to suppress insulin biosynthesis, but probucol treatment led to preservation of beta-cell mass and the insulin content. According to intraperitoneal glucose tolerance tests, the probucol treatment preserved glucose-stimulated insulin secretion and improved glucose tolerance at 10 and 16 weeks: insulin, 280+/-82 vs. 914+/-238 pmol/l (120 min, at 16 weeks; $P<0.05$); glucose, 44.6+/-2.4 vs. 35.2+/-2.6 mmol/l (120 min, at 16 weeks; $P<0.05$). Thus, our present observations demonstrate the potential usefulness of probucol for treatment of type 2 diabetes." Thus, it was known in the art at the time of the invention that antioxidants having anti-lipidemic effect and glucose tolerance inhibiting effect, such as the berberine extracted from Coptis used in the method taught by Song, preserve insulin beta-cell content and lower

serum blood levels; and thereby suggest the use of antioxidant therapy for the treatment of non-insulin dependent diabetes.

Thirdly, Hamaoka teaches that overexpression of aldose reductase in pancreatic beta-cells induced by superoxidase dismutase promotes apoptosis and suggests the use of aldose reductase inhibitors for the treatment and pathogeneses of diabetic complications. Thus, it was suggested in the art at the time the invention was made that aldose reductase inhibitors, such as the catalpol extracted from *Rehmanniae* and having beneficial effects in ameliorating diabetic complications taught by Nishimura, lower apoptosis of insulin beta-cells of islets; and thereby is useful in the treatment and complications associated with Type II diabetes.

Given the teachings of the references as a whole, an artisan of ordinary skill would have had a reasonable expectation that combining the berberine, as used in the methods taught by Jiang and Song, with the catalpol taught by Nishimura would be successful in providing a method of treating non-insulin dependent diabetes comprising a step of administering to said living object a composition comprising a predetermined amount of berberine as a first active ingredient and a predetermined amount of catalpol as a second active ingredient, in such a manner that when said first and said active ingredients are administered, insulin beta cells of said living object is substantially restored so as to achieve lowering of plasma sugar level. This reasonable expectation of success would have motivated the artisan to use the ingredients taught by the combined teachings of Jiang, Song and Nishimura to arrive at the instantly claimed

invention, given the beneficial functional effects for each of berberine and catalpol that they have shown in the treatment of Type II diabetes.

The references do not specifically teach using the composition in the amounts claimed by Applicant. The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). However, the references teach that the amounts of berberine and catalpol can be varied. Thus, the combined teachings of Jiang, Song and Nishimura recognize that the amount of the claim-designated ingredients can be modified. Therefore, it would have been customary for an artisan of ordinary skill to determine the optimal amount of the ingredient to add in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount would have been obvious at the time of Applicant's invention.

With regard to the claim limitations of each of Claims 60-64 wherein Applicant directs the instantly claimed method to a composition prepared as either a draught in water, a syrup, a cachet and a solution, it also would have been *prima facie* obvious to one of ordinary skill in the art practicing the invention to modify the form of the composition taught by the combined references by preparing the composition as either a draught in water, a syrup, a cachet or a solution to provide the instantly claimed method because at the time the invention was made each of the claim-designated

pharmaceutical forms were known to be conventional and useful vehicles for the delivery of an anti-diabetic agent for the treatment of non-insulin diabetes mellitus. Therefore, one of ordinary skill in the art would have been motivated and had a reasonable expectation that such a modification of the teachings would be successful.

As the references indicate that the various proportions and amounts of the ingredients used in the claimed method are result effect variables, they would have been routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by the references.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Claims 51-56, 66 and 68-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jiang et al. (O or U; Translation of foreign patent document CN 1393264 A provided herein and referred to herein.) and Song et al. (V; Translation of foreign language document provided herein.) and Nishimura et al. (R) in view of Yoshikawa et al. (U1), and further in view of Ebrup et al. (O), Gorogawa et al. (W) and Hamaoka et al. (X).

Applicant's claimed invention was set forth above.

The combined teachings of Jiang, Song and Nishimura made obvious over the teachings of Ebrup, Gorogawa and Hamaoka are set forth above. The combined references teach the instantly claimed invention except for oleanolic acid. However, it

would have been obvious to one of ordinary skill in the art to add the claim-designated ingredient to the method of treatment taught by the combined references because at the time the invention was made Yoshikawa taught an oleanolic acid obtained from *Beta vulgaris* exhibiting hypoglycemic activity in oral glucose tolerance test in rats. Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add the claimed ingredient in the making of the claimed method of treating non-insulin dependent diabetes in a subject in need thereof because it is well known that its *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten*, 459 F. 2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi*, 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960).

The references do not specifically teach using the composition in the amounts claimed by Applicant. The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). However, the references teach that the amounts of berberine and catalpol can be varied. Thus, the combined teachings of Jiang, Song and Nishimura recognize that the amount of the

claim-designated ingredients can be modified. Therefore, it would have been customary for an artisan of ordinary skill to determine the optimal amount of the ingredient to add in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount would have been obvious at the time of Applicant's invention.

With regard to the claim limitations of each of Claims 69-73 wherein Applicant directs the instantly claimed method to a composition prepared as either a draught in water, a syrup, a cachet and a solution, it also would have been *prima facie* obvious to one of ordinary skill in the art practicing the invention to modify the form of the composition taught by the combined references by preparing the composition as either a draught in water, a syrup, a cachet or a solution to provide the instantly claimed method because at the time the invention was made each of the claim-designated pharmaceutical forms were known to be conventional and useful vehicles for the delivery of an anti-diabetic agent for the treatment of non-insulin diabetes mellitus. Therefore, one of ordinary skill in the art would have been motivated and had a reasonable expectation that such a modification of the teachings would be successful.

As the references indicate that the various proportions and amounts of the ingredients used in the claimed method are result effect variables, they would have been routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by the references.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is 571-272-0964. The examiner can normally be reached on 7:00 am - 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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MCF

January 4, 2009

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